CASE REPORT

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Valproic Acid-induced Bilateral Irreversible Hearing Loss

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ABSTRACT Valproic acid (VPA) is a widely used drug in the field of neuro-pschiatry for the treatment of various types of epilepsy, as prophylaxis for migraine headaches, and in the treatment and prevention of manic attacks related to bipolar disorder. Ototoxicity related to VPA is very rare and only a few cases have been reported in the literature. In this case report, a 21-year old male patient admitted to our clinic with the complaint of bilateral sudden total hearing loss associated with VPA is presented. The patient had a history of moderate hearing loss before initiation of VPA and on the second day of his VPA treatment, a further reduction in his hearing levels occurred. At the end of the third day, the total hearing loss had developed which did not respond to treatment and became permanent.

Keywords: Valproic acid; ototoxicity; irreversible sensorineural hearing loss; sudden hearing loss

Ototoxicity is one of the well-known causes of sensorineural type hearing loss induced by drugs or chemical substances reaching the inner ear. It generally occurs with damage to the sensorial cells in the cochlea. This damage may be reversible or permanent. The toxic substance which is responsible for the etiology of ototoxicity reaches the inner ear via the blood circulation and causes hearing loss mostly in both ears.

Valproic acid (VPA) is a widely used drug in the field of neuro-pschiatry for the treatment of various types of epilepsy, as prophylaxis for migraine headaches, and in the treatment and prevention of manic attacks related to bipolar disorder. Ototoxicity related to VPA is very rare and only a few cases have been reported in the literature. In the previous reports with VPA induced ototoxicity, all patients had pre-existing reduced hearing levels which were exacerbated by VPA, and the following cessation of the drug a return to previous levels of the hearing was observed in a short period except one patient. In some cases, the hearing loss developed gradually within a month after initiation of VPA, and recovery over time was observed following cessation of the drug.[1] However, patients with a sudden reduction in hearing with the use of VPA that were improved within hours of cessation of the drug were also reported.[2]

In this case, we present a patient with a history of hearing loss since birth who has not used any hearing devices. The patient has been taking medication for many years with the diagnosis of bipolar disorder. Three months ago, VPA has been started and within 3 days after initiation of the drug, the patient experienced a complete loss of hearing in both ears. The VPA was discontinued and treatment for sudden hearing loss was begun. However, hearing loss could not be regained.

CASE REPORT

A 21-year old male patient presented with the complaint of bilateral complete hearing loss. He had a history of a moderate level sensorineural hearing loss, mostly involving high frequencies, since birth. A reg-

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ular, yearly follow-up of hearing levels with a hearing test obtained from his medical records (Figure 1). There was no history of hearing device use. Also, the patient had a history of diagnosis of bipolar disorder which was followed up by a psychiatrist. He has been taking medications for his bipolar disorder for a long time. Three days before his admittance to our clinic, he was examined in the psychiatry department and treatment of oral VPA (Depalex XR 500 mg), which has not been used before, was initiated. On the day after starting VPA, the patient noticed a reduction in his hearing, and within 3 days of complete hearing loss occurred. VPA has been ceased immediately, and the patient was referred to our clinic.

There was no dizziness, tinnitus, or a history of head trauma. In the physical examination, the external ear canals and tympanic membranes were normal in both ears. In the audiological evaluation, a total sensorineural hearing loss involving all frequencies was observed. The mean pure-tone hearing threshold was evaluated as 120 dB bilaterally and the speech discrimination test could not be taken (Figure 2). BERA was performed to the patient and waves could not be detected bilaterally (Figure 3). No pathology was seen on the internal acoustic canal magnetic resonance imaging (MRI), the brain MRI, and inner ear computer tomography CT) examinations. Routine blood tests were also noted as normal.

Steroid therapy was started for the treatment of sudden hearing loss, beginning with intravenous prednisolone (Prednol 250 mg), followed by oral prednisolone starting at a 60 mg dose tapering over 3 days. As no response was obtained at the end of 3 days of steroid therapy, hyperbaric oxygen was added to the therapy. At the end of 2 weeks, no improvement was seen in the hearing levels of the patient. The patient still had bilateral total hearing loss at the end of 2.5 months after the therapy and did not benefit from the hearing device. The cochlear implant surgery was planned but the patient refused the surgery.

Informed consent form and permission for the academic publication were received from the patient.

DISCUSSION

Ototoxicity occurs as structural or functional damage in the inner ear because of a chemical substance af-

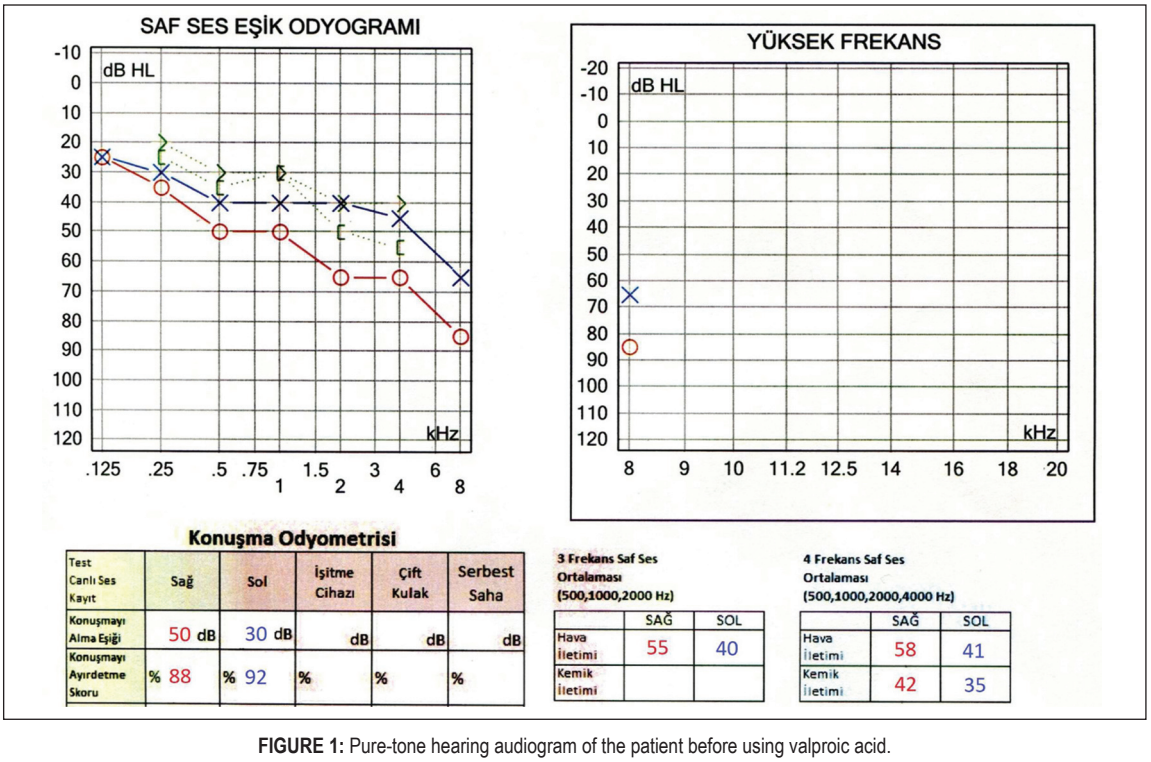

FIGURE 1: Pure-tone hearing audiogram of the patient before using valproic acid.

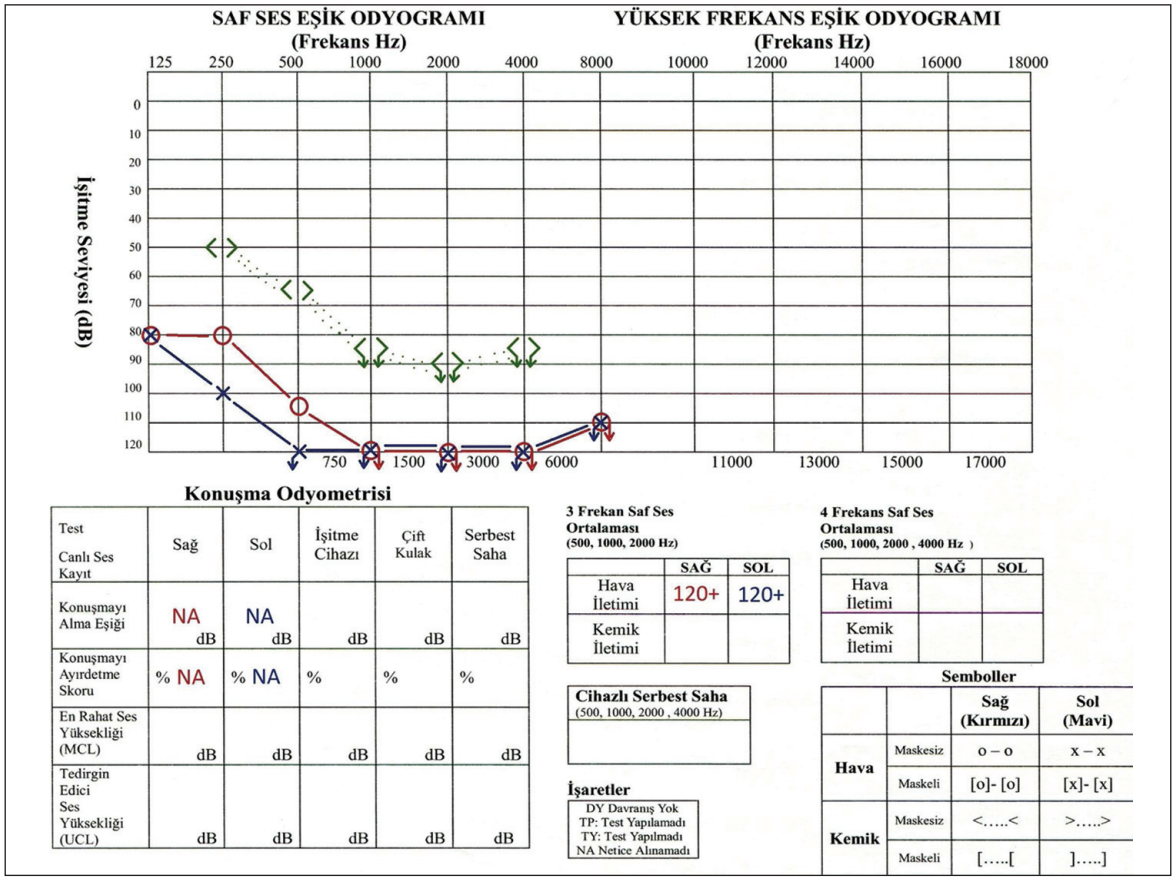

FIGURE 2: Pure-tone hearing audiogram of the patient after using valproic acid.

fecting the inner ear. This damage may be reversible or permanent. A high possibility of ototoxicity associated with the side effects of some drugs is well known in the literature. Although this possibility is as high as 5-10% in aminoglycoside group antibiotics, it is not expected at high rates in some drugs such as VPA. Only, few cases of hearing loss developing after VPA administration have been reported in the literature.

In 1990, Armon et al. reported 2 patients both over 70 years old. Patients had previously reduced hearing because of presbyacusis; however, they experienced an increased loss of hearing after the use of VPA, which then recovered one month following termination of the drug.[1]

Hori et al. presented a case of a 9-year old child with advanced hearing loss since birth (on the right-side total, on the left-side 76 dB). After initiation of VPA because of epilepsy, the hearing was completely lost within 3 months but then started to recover at 6 weeks following termination of VPA use (83 dB). However, in subsequent days, hearing of the patient has deteriorated again, and no improvement was seen in the following 2 years.[2]

Yeap et al. reported a 39-year old patient with a hearing loss at high frequencies because of acoustic trauma associated with his occupation as a lorry driver. The patient's hearing loss was related to VPA use which was demonstrated with audiometry and BERA tests that were performed before and after administration of the drug. The reduction in hearing levels recovered within hours following the termination of the drug.[3]

All cases in the literature, along with our case, had already reduced hearing and VPA exacerbated this already existed hearing loss. In some cases, this effect occurred immediately after taking the drug; however, in some cases, it developed slowly over time. In our

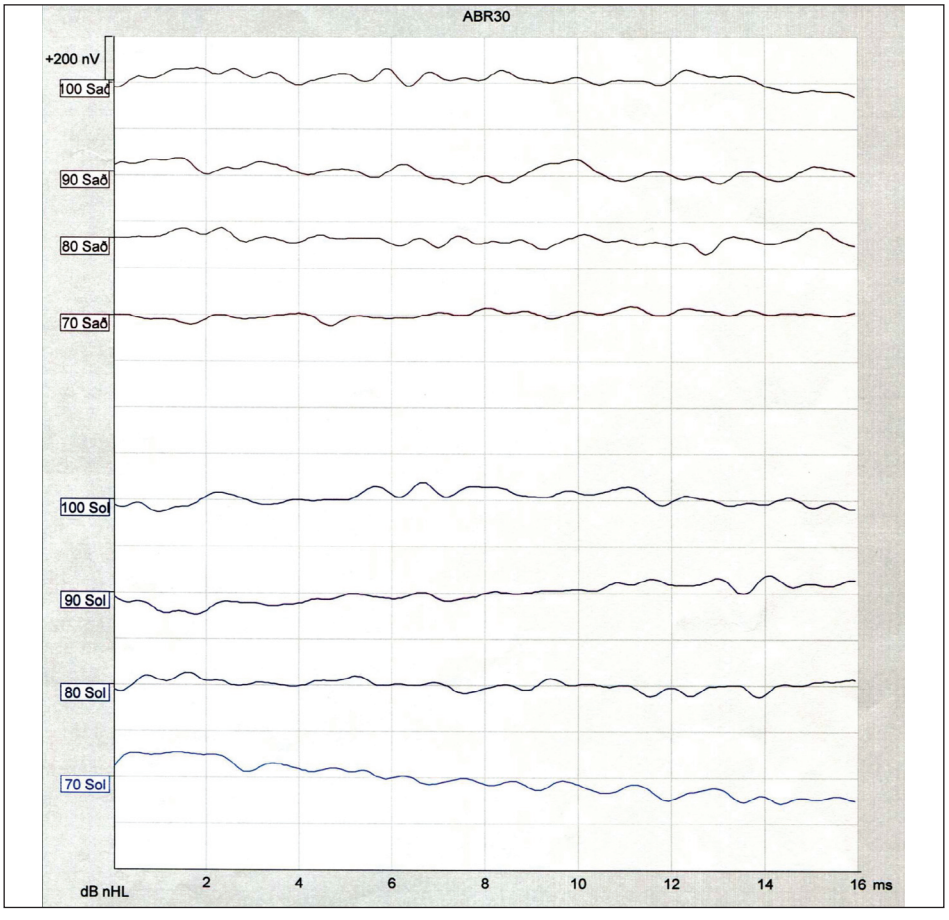

FIGURE 3: Bilaterally brainstem waves were not detected in the BERA examination.

case, the hearing loss started one day after initiation of VPA, and hearing was completely lost in 3 days on both ears. Also, both ears were affected in all of the reported cases in the literature. All cases in the literature, except one case, recovered their drug-related hearing loss following termination of VPA, and the previous levels of hearing were achieved. In our case, the hearing loss did not recover and became permanent, and seems to be the second case reported in the literature.[2] In our case, the hearing thresholds before initiation of VPA were better (on the right-side 55dB, on the left-side 40dB) according to the case presented by Hori et al. and total hearing loss developed subsequently in both ears (120 dB).

Data in the literature reveals that the use of VPA does not affect hearing in patients with normal hearing levels. Supporting this theory, Incecik et al. showed that there was no negative effect of VPA on hearing levels in patients with normal hearing.[4]

The mechanism of the effect of VPA is formed through the inhibition of excitatory neurons and a reduction in glutamate expression by reducing the passage of sodium into neurons. The pathophysiology of ototoxicity associated with VPA use is not fully known. It may be caused by damage in the hair cells which transform mechanical sound waves in the cochlea to electrical energy, or by neural damage that impairs electrical transmission.[4] Further studies may clarify this mechanism in the future. The recovery of hearing loss in some patients suggests that the ototoxic effect of VPA could be time and dose-related.

In conclusion, VPA has a potential side effect leading to deterioration in hearing levels in patients with pre-existing hearing loss. Therefore, if VPA is to be prescribed in patients with a known history of hearing loss, close follow up of hearing levels is mandatory and it would be appropriate to cease the drug if reduced hearing exists.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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